# Part II

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Mobic 7.5 mg Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 7.5 mg meloxicam.

*For a full list of excipients, see section 6.1.*

## 3 PHARMACEUTICAL FORM

Tablet.

Light yellow round tablets with the logotype of the company on one side and a score with ‘59D/59D’ on the other side.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

- Short-term symptomatic treatment of exacerbations of osteoarthrosis.
- Long term symptomatic treatment of rheumatoid arthritis or ankylosing spondylitis.

### 4.2 Posology and method of administration

- Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms *(see section 4.4).*
- Exacerbations of osteoarthritis : 7.5 mg/day (one 7.5 mg tablet). If necessary, in the absence of improvement, the dose may be increased to 15 mg/day (two 7.5 mg tablets).
- Rheumatoid arthritis, ankylosing spondylitis: 15mg/day (two 7.5 mg tablets).*(See also ‘special precautions’).*

According to the therapeutic response, the dose may be reduced to 7.5mg/day (one 7.5 mg tablet).

DO NOT EXCEED THE DOSE OF 15 MG/DAY.

The total daily amount should be taken as a single dose, with water or another liquid, during a meal.

**Special populations**

Elderly patients with increased risks for adverse reactions *(see section 5.2):*
The recommended dose for long term treatment of rheumatoid arthritis and ankylosing spondylitis in elderly patients is 7.5 mg per day. Patients with increased risks for adverse reactions should start treatment with 7.5 mg per day *(see section 4.4).*

Renal impairment *(see section 5.2):*
In dialysis patients with severe renal failure, the dose should not exceed 7.5 mg per day.

No dose reduction is required inpatients with mild to moderate renal impairment (i.e. patients with a creatinine clearance of greater than 25ml/min). *(For patients with non-dialysed severe renal failure, see section 4.3).*

Hepatic impairment *(see section 5.2):*
No dose reduction is required in patients with mild to moderate hepatic impairment *(for patients with severely impaired liver function, see section 4.3)*

Children:
Mobic should not be used in children aged under 15.

This medicinal product exists in other dosages, which may be more appropriate.

## 4.3 Contraindications

This medicinal product is contra-indicated in the following situations:

- Pregnancy and lactation *(See section Pregnancy and lactation)*

- Hypersensitivity to meloxicam or to one of the excipients or hypersensitivity to substances with a similar action, e.g. NSAIDs, aspirin. Mobic should not be given to patients who have developed signs of:
  - asthma, nasal polyps, angioneurotic oedema or urticaria following the administration of aspirin or other NSAIDs.
  - active gastrointestinal ulcer or history of recurrent gastrointestinal ulcer
  - active peptic ulcer or history of recurrent peptic ulcer;
  - severely impaired liver function;
  - non-dialysed severe renal failure;
  - gastrointestinal bleeding, cerebrovascular bleeding or other bleeding disorders.

- This product includes lactose: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy. Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

- Severe heart failure.

## 4.4 Special warnings and precautions for use

The use of Mobic may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of Mobic should be considered.

The use of Mobic with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

Elderly: The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal *(see section 4.2).*

Gastrointestinal bleeding, ulceration and perforation: GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation *(see section 4.3),* and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk *(see below and 4.5).*

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin *(see section 4.5).*

When GI bleeding or ulceration occurs in patients receiving Mobic, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated *(see section 4.8 – Undesirable effects).*

Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported rarely in association with the use of NSAIDs *(see 4.8).* Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Mobic should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Undesirable effects may be minimized by using the minimum effective dose for the shortest duration necessary to control the symptoms *(see section 4.2, and GI and cardiovascular risks below).*

***Cardiovascular and cerebrovascular effects***

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that the use of coxibs and some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for meloxicam.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should not be treated with meloxicam after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, and smoking).

Any history of oesophagitis, gastritis and/or peptic ulcer must be sought in order to ensure their total cure before starting treatment with meloxicam. Attention should routinely be paid to the possible onset of a recurrence in patients treated with meloxicam and with a past history of this type.

Patients with gastrointestinal symptoms or history of gastrointestinal disease should be monitored for digestive disturbances, especially for gastrointestinal bleeding.

As with other NSAIDs, gastrointestinal bleeding or ulceration/perforation, in rare cases fatal, have been reported with meloxicam at any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events. Gastrointestinal bleeding or ulceration/perforation has in general more serious consequences in the elderly *(see section 4.8).*

If gastrointestinal bleeding or ulceration occurs in patients receiving meloxicam, the drug should be withdrawn.

The possibility occurrence of severe skin reactions and serious life threatening hypersentivity reactions (i.e. anaphylactic reactions) is known to occur with NSAIDs including oxicams. In those cases, Meloxicam should be withdrawn immediately and careful observation is necessary.

In the rare instance NSAIDs may be the cause of interstitial nephritis, glomerulonephritis, renal medullary necrosis or

nephrotic syndrome.

As with most NSAIDs, occasional increases in serum transaminase levels, increases in serum bilirubin or other liver function parameters, as well as increases in serum creatinine and blood urea nitrogen as well as other laboratory disturbances, have been reported. The majorityof these instances involved transitory and slight abnormalities. Should any such abnormality prove significant or persistent, the administration of Meloxicam should be stopped and appropriate investigations undertaken.

Induction of sodium, potassium and water retention and interference with the natriuretic effects of diuretics and consequently possible exacerbations of the condition of patients with cardiac failure or hypertension may occur with NSAIDs. *(See sections 4.2 and 4.3)*

NSAIDs inhibit the synthesis of renal prostaglandins involved in the maintenance of renal perfusion, in patients with decreased renal blood flow and blood volume. Administration of NSAIDs in such situations may result in the decompensation of latent renal failure. However, renal function returns to its initial status when treatment is withdrawn. This risk concerns all elderly individuals, patients with congestive cardiac failure, cirrhosis, nephrotic syndrome or renal failure as well as patients on diuretics or having undergone major surgery leading to hypovolemia. Careful monitoring of diuresis and renal function during treatment is necessary in such patients. *(see sections 4.2 and 4.3)*

Adverse reactions are often less well tolerated in elderly, fragile or weakened individuals, who therefore require careful monitoring. As with other NSAIDs, particular caution is required in the elderly, in whom renal, hepatic and cardiac functions are frequently impaired.

The recommended maximum daily dose should not be exceeded in case of insufficient therapeutic effect, nor should an additional NSAID be added to the therapy because this may increase the toxicity while therapeutic advantage has not been proven. In the absence of improvement after several days, the clinical benefit of the treatment should be reassessed.

Meloxicam, as any other NSAID, may mask symptoms of an underlying infectious disease.

The use of Meloxicam, as with any drug known to inhibit cyclooxygenase /prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of Meloxicam should be considered.

## 4.5 Interaction with other medicinal products and other forms of interaction

Corticosteroids: increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin *(see section 4.4).*

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding *(see section 4.4).*

**Pharmacodynamic Interactions:**

**Other NSAIDs, including salicylates (acetylsalicylic >3g/d):**
Administration of several NSAIDs together may increase the risk of gastrointestinal ulcers and bleeding, via a synergistic effect. The concomitant use of Meloxicam with other NSAIDs is not recommended *(see section 4.4)*

**Diuretics** :
Treatment with NSAIDs is associated with potential for acute renal failure in dehydrated patients. Patients receiving Meloxicam and a diuretic should be adequately hydrated and be monitored for renal function prior to initiating treatment *(see section 4.4).*

**Oral anticoagulants**
Increased risk of bleeding, via inhibition of platelet function and damage to the gastroduodenal mucosa. The

concomitant use of NSAIDs and oral anticoagulants is not recommended *(see section 4.4).*

Careful monitoring of the INR is required if it proves impossible to avoid such combination.

**Thrombolytics and antiplatelet drugs:**
Increased risk of bleeding via inhibition of platelet function and damage to the gastrointestinal mucosa.

**ACE inhibitors and angiotensin II receptor antagonists:**
NSAIDs (including acetylsalicylic acid at dose >3g/d) and angiotensin-II receptor antagonist exert a synergistic effect on the decreases of glomerular filtration, which may be exacerbated when renal function is altered. When given to the elderly and/or dehydration patients, this combination can lead to acute renal failure by acting directly on glomerular flirtation monitoring of renal function at the beginning of the treatment is recommended as well as regular hydration of the patients. Additionally, concomitant treatment can reduce antihypertensive effects of ACE inhibitors and angiotensin II receptor antagonists, leading to partial loss of efficacy (due to inhibition of prostaglandins with vasodilatory effects).

**Antihypertensive drugs (e.g. beta-blockers):**
As for the latter, a decreased of the antihypertensive effect of beta blockers (due to inhibition of prostaglandins with vasodilatory effect) can occur.

**Cyclosporin**: Nephrotoxicity of cyclosporin may be enhanced by NSAIDs via renal prostaglandin mediated effects. During combined treatment, renal function is to be measured. A careful monitoring of the renal function is recommended, especially in the elderly.

**Intrauterine devices:**
NSAIDs have been reported to decrease the efficacy of intrauterine devices. A decreased of the efficacy of intrauterine devices by NSAIDs has been previously reported but needs further confirmation.

**Pharmacokinetic Interactions (effect of meloxicam on the pharmacokinetic of other drugs)**

**Lithium:**
NSAIDs have been reported to increase blood lithium levels (via decreased renal excretion of lithium) which may reach toxic values. The concomitant use of lithium and NSAIDs is not recommended *(see section 4.4).* if this combination appears necessary, lithium plasma concentrations should be monitored carefully during the initiation, adjustment and withdrawal of meloxicam treatment.

**Methotrexate**:
NSAIDs can reduce the tubular secretion of methotrexate theraby increasing the plasma concentrations of methotrexate. For this reason, for patients on high dosage of methotrexate (more than 15mg/week) concomitant use of NSAIDs is not recommended *(see section 4.4).*

The risk of an interaction between NSAIDs preparation and methotrexate should be considered also in patients on low dosage of methotrexate, especially in patients with impaired renal function. In cases combination treatment is necessary blood cell count and the renal function should be monitored. Caution should be taken in case both NSAIDs and methotrexate are given within 3 days, in which case the plasma level of methotrexate may increase and cause increased toxicity.

Although the pharmacokinetics of methotrexate (15mg/week) were not relevantly affected by concomitant meloxicam treatment, it should be considered that the haematological toxicity of methotrexate can be amplified by treatment with NSAIDs drugs (see above). *(see section 4.8).*

**Pharmacokinetic Interactions (effected of other drugs on the pharmacokinetic of meloxicam**)

**Cholestyramine:**
Cholestryamine accelerates the elimination of meloxicam by interrupting the enterohepatic circulation so that clearance for meloxicam increases by 50% and the half-life decreases to 13+3 hrs. This interaction is of clinical significance.

No clinical relevant pharmacokinetic drug-drug interactions were detected with respect to the concomitant administration of antacids, cimetidine and digoxin.

## 4.6 Pregnancy and lactation

**Pregnancy**

- In animals, lethal effects on the embryo have been reported at doses higher than those used clinically.
- It is advisable to avoid the administration of meloxicam during pregnancy.
- During the final three months, all prostaglandin synthesis inhibitors may expose the foetus to cardiopulmonary (pulmonary hypertension with premature closure of the ductus arteriosus) and renal toxicity or inhibit the contraction of the uterus. This effect on the uterus has been associated with an increase in the incidence of dystocia and delayed parturition in animals. Thus all NSAIDs are absolutely contra-indicated during the final three months.

**Lactation**

- NSAIDs pass into mothers' milk. Administration should therefore be avoided, as a precautionary measure, in women who are breast feeding.

## 4.7 Effects on ability to drive and use machines

There are no specific studies on the ability to drive and use machinery. However, on the basis of the Pharmacodynamic profile and reported adverse drug reactions, meloxicam is likely to have no or negligible influence on these abilities.

However when visual disturbances or drowsiness, vertigo or other central nervous system disturbances occur, it is advisable to refrain from driving and operating machinery.

## 4.8 Undesirable effects

*Gastro-intestinal*: The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur *(see section 4.4).*

Nausea, vomiting, diarrhea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease *(see section 4.4 – Special warnings and precautions for use)* have been reported following administration. Less frequently, gastritis has been observed.

Bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis (very rare).

Oedema, hypertension and cardiac failure, have been reported in association with NSAID treatment.

Clinical trial and epidemiological data suggests that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) *(see section 4.4)*

**a) General Description**

The following adverse events, which may be casually related to the administration of meloxicam, have been reported. The frequencies given below are based on corresponding occurrences in clinical trials, regardless of any causal relationship. The information is based on clinical trials involving 3750 patients who have been treated with daily oral doses of 7.5 or 15 mg meloxicam tablets or capsules over a period of up to 18 months (mean duration of treatment 127 days).

Adverse events which may be casually related to the administration of meloxicam that have come to light as a result of reports received in relation to administration of the marketed product are included.

Adverse reactions have been ranked under heading of frequency using the following convention:

Very common (>1/10); common (>1/100); uncommon (>1/1000, <1/100); rare (>1/10000, <1/1000) very rare (<1/10000)

**b) Table of adverse reactions**

Blood and the lymphatic system disorders

Common: Anaemia
Uncommon: Disturbances of blood count: leucocytopenia; thrombocytopenia; agranulocytosis (see section c)

Immune system disorders
Rare: anaphylactic/ anaphylactoid reactions

Psychiatric disorders
Rare: mood disorders, insomnia and nightmares

Nervous system disorders
Common: lightheadedness, headache
Uncommon; vertigo, tinnitus, drowsiness
Rare: confusion

Eye disorders
Rare: visual disturbances including blurred vision

Cardiac disorders
Uncommon: palpitations

Vascular disorders
Uncommon: increase in blood pressure *(see section 4.4)*, flushes

Respiratory, thoracic and mediastinal disorders
Rare: Onset of asthma attacks in certain individuals allergic to aspirin or other NSAIDs

Gastrointestinal disorders
Common: dyspepsia, nausea and vomiting symptoms, abdominal pain, constipation, flatulence, diarrhoea

Uncommon: gastrointestinal bleeding, peptic ulcers, oesophagitis, and stomatitis

Rare: gastrointestinal perforation, gastritis, colitis the peptic ulcers, perforation or gastrointestinal bleeding, that may occur can be sometimes severe, especially in elderly *(see section 4.4).*

Hepato-biliary disorders
Uncommon: transitory disturbances of liver function test (e.g. raised transaminases or bilirubin)

Rare: hepatitis

Skin and subcuntaneous tissue disorders
Common: pruritus, rash
Uncommon: urticaria
Rare: Stevens-Johnson syndrome and toxic epidermal necrolysis, angiodema, bullous reaction such as erythema multiforme, photosensitivity reactions

Renal and urinary disorders
Uncommon: Disturbances of laboratory tests investigating renal function (e.g. raised creatinine or urea)
Rare: Renal failure *(see section 4.4)*

General disorders and administration site conditions
Common: oedema including oedema of the lower limbs.

**c) Information characterizing Individual Serious and/ or Frequently Occurring Adverse Reactions**
Isolated cases of agranulocytosis have been reported in patients with meloxicam and other potentially myelotoxic drugs *(see section 4.5)*

## 4.9 Overdose

Symptoms following acute NSAIDs overdose are usually limited to lethargy, drowsiness, nausea, vomiting and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Severe poisoning may result in hypertension, acute renal failure, hepatic dysfunction, respiratory depression, coma, convulsions, cardiovascular collapse and cardiac arrest. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs and may occur following an overdose.

Patients should be managed with symptomatic and supportive care following an NSAIDs overdose. Accelerated removal of meloxicam by 4g oral doses of cholestyramine given three times a day was demonstrated in a clinical trial.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

**Pharmacetherapeutic group:** Non-steroidal anti-inflammatory agent, Oxicam
**ATC Code:** M01AC06

Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the enolic acid class, which has shown anti-inflammatory, analgesic and antipyretic properties.

The anti-inflammatory activity of meloxicam has been proven in classical models of inflammation. As with other NSAIDs, its precise mechanism of actions remains unknown. However, there is at least one commen mode of action shared by all NSAIDs (including Meloxicam): inhibition of the biosynthesis of prostaglandins, known mediators of inflammation.

## 5.2 Pharmacokinetic properties

**Absorption**
Meloxicam is well absorbed from the gastrointestinal tract, which is reflected by a high absolute bioavailability of 89% following oral administration (capsule). Tablets, oral suspension and capsules were shown to be bioequivalent

Following single dose administration of meloxicam, mean plasma concentrations are achieved within 2 hours for the suspension and within 5-6 hours with solid oral dosage forms (capsules and tablets).

With multiple dosing, steady state conditions were reached within 3 to 5 days. Once daily dosing leads to drug plasma concentrations with a relatively small peak-trough fluctuation in the range of 0.4-1.0 µg/mL for 7.5 mg dose and 0.8-2.0µg/mL for 15 mg dose, respectively ($C_{min}$ and $C_{max}$ at steady state, respectively). Maximum plasma concentration of meloxicam at steady state, are achieved within five to six hours for the tablet, capsule and the oral suspension, respectively. Continuous treatment for periods of more than one year result in similar drug concentrations to meloxicam following oral administration is not altered by concomitant food intake.

**Distribution**
Meloxicam is very strongly bound to plasma proteins, essentially albumin (99%). Meloxicam penetrates into synovial to give concentrations approximately half of those in plasma.

Volume of distribution is low, on average 11L. interindividual variation is the order of 30-40%.

**Biotransformation**
Meloxicam undergoes extensive hepatic biotransformation. Four different metabolites of meloxicam were identified in urine, which are all pharmacodynamically inactive. The major metabolite, 5'-carboxymeloxicam (60% of dose), is formed by oxidation of an intermediate metabolite 5'-hydroxymethylmeloxicam, which is also excreted to a lesser extent (9% dose). In vitro studies suggest that CYP 2C9 plays an important role in this metabolite pathyway, with a minor contribution from the CYP 3A4 isoenzyme. The patient's peroxidase activity is probably responsible for the other two metabolites, which account for 16% and 4% of the administered dose respectively.

**Eliminate**
Meloxicam is excreted predominantly in the form of metabolites and occurs to equal extents in urine and faeces. Less than 5% of the daily dose is excreted unchanged in faeces, while only traces of the parent compound are excreted in urine.

The mean elimination half-life is about 20 hours. Total plasma clearance amounts on average 8 mL/min.

**Linearity/non-linearity :**
Meloxicam demonstrations liner pharmacokinetic in the therapeutic dose range of 7.5mg 15mg following per oral or intramuscularly administration.

**Special populations :**

Hepatic/renal Insufficiency:
Neither hepatic, mild nor moderate renal insufficiency has a substantial effect on meloxicam pharmacokinetics. In terminal renal failure, the increase in the volume of distribution may result in higher free meloxicam concentrations, and a daily dose of 7.5 mg must not be exceeded *(see section 4.2).*

Elderly:
Mean plasma clearance at steady state in elderly subjects was slightly lower than that reported for younger subjects.

## 5.3 Preclinical safety data

The toxicological profile of Meloxicam has been found in preclinical studies to be identical to that of NSAIDs: gastrointestinal ulcers and erosions, renal papillary necrosis at high doses during chronic administration in two animal species.

Oral reproductive studies in the rat have shown a decrease of ovulations and inhibition of implantations and embryotoxic effects (increase of resorptions) at maternotoxic dose levels at 1 mg/kg and higher.

The affected dose levels exceeded the clinical dose (7.5-15 mg) by a factor of 10 to 5-fold on a mg/kg dose basis (75 kg person).

Fetotoxic effects at the end of gestation, shared by all prostaglandin synthesis inhibitors, have been described. No evidence has been found of any mutagenic effect, either in vitro or in vivo.

No carcinogenic risk has been found in the rat and mouse at doses far higher than those used clinically.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Sodium citrate
Lactose monohydrate
Microcrystalline cellulose
Povidone
Anhydrous colloidal silica
Crospovidine

Magnesium stearate

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf Life

The shelf-life expiry date of this product shall be the date shown on the container and outer package on the market in the country of origin.

## 6.4 Special precautions for storage

Do not store above 25°C
Store in the original package.

## 6.5 Nature and contents of container

Blister packs of 20 or 30 tablets in a cardboard carton.

## 6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

None.

## 7 PARALLEL PRODUCT AUTHORISATION HOLDER

PCO Manufacturing Limited
Unit 10, Ashbourne Business Park
Rath
Ashbourne
Co. Meath

## 8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 0465/112/001

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 January 2004

## 10 DATE OF REVISION OF THE TEXT

October 2008